L Number	Hits	Search Text	DB	Time stamp
1	290	(parathyroid adj hormone adj receptor$) or (pth adj receptor)	USPAT; US-PGPUB; EPO; DERWENT	2004/05/11 16:27
2	65	((parathyroid adj hormone adj receptor$) or (pth adj receptor)) with (agonist$ or antagonist$)	USPAT; US-PGPUB; EPO; DERWENT	2004/05/11 16:28
3	30	(((parathyroid adj hormone adj receptor$) or (pth adj receptor)) with (agonist$ or antagonist$)) same (method or assay$ or screen$)	USPAT; US-PGPUB; EPO; DERWENT	2004/05/11 16:28

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=> s (parathyroid(w)hormone(w)receptor?) or (pth(w)receptor?)
L1         3491 (PARATHYROID(W) HORMONE(W) RECEPTOR?) OR (PTH(W) RECEPTOR?)

=> s l1(s)(agonist? or antagonist?)
L2          375 L1(S)(AGONIST? OR ANTAGONIST?)

=> s l2(p)(method or assay? or screen?)
L3          122 L2(P)(METHOD OR ASSAY? OR SCREEN?)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4          102 DUP REM L3 (20 DUPLICATES REMOVED)

=> s l4 and py<=2000
   3 FILES SEARCHED...
L5           53 L4 AND PY<=2000

=> d ibib abs 1-53

L5   ANSWER 1 OF 53   MEDLINE on STN
ACCESSION NUMBER:    96117061      MEDLINE
DOCUMENT NUMBER:     PubMed ID: 8544835
TITLE:               Homolog-scanning mutagenesis of the parathyroid hormone
                     (PTH) receptor reveals PTH-(1-34) binding determinants in
                     the third extracellular loop.
AUTHOR:              Lee C; Luck M D; Juppner H; Potts J T Jr; Kronenberg H M;
                     Gardella T J
CORPORATE SOURCE:    Endocrine Unit, Massachusetts General Hospital, Boston
                     02114, USA.
SOURCE:              Molecular endocrinology (Baltimore, Md.), (1995
                     Oct) 9 (10) 1269-78.
                     Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199602
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ENTRY DATE: Entered STN: 19960227
Last Updated on STN: 19960227
Entered Medline: 19960213

AB To identify determinants in the rat **PTH receptor** critical for binding the **agonist** peptide, PTH-(1-34), we systematically replaced 12 segments (5-33 residues) of the receptor's extracellular surface with the corresponding segments of the homologous rat secretin receptor and **screened** the resulting mutants in COS-7 cells for altered PTH-(1-34) binding properties. Surface expression of mutant receptors was assessed by the binding of monoclonal antibody 12CA5 to the epitope (HA)-tagged receptors. Of the nine well expressed and therefore informative receptor mutants, four bound radiolabeled PTH-(1-34) at levels that were proportional to the corresponding levels of surface expression, whereas five mutants bound [125I]PTH-(1-34) to levels that were lower than predicted from the cell surface expression levels. These five mutations occurred at the extracellular (EC) end of transmembrane domain 1, the carboxy-terminal portion of the first EC loop, the second EC loop, and the third EC loop. We selected for further fine structure analysis the third EC loop; two specific residues, Trp-437 and Gln-440, were identified at which mutations caused 9- to 16-fold reductions in PTH-(1-34)-binding affinity. The same mutations had little or no effect on the binding affinity of PTH-(3-34). This study provides new information on the location of **PTH receptor** regions important for high affinity **agonist** binding and identifies two residues in the third extracellular loop which may contribute to interactions involving the hormone's critical amino terminus.

L5 ANSWER 2 OF 53 MEDLINE on STN
ACCESSION NUMBER: 94349874 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8070362
TITLE: Determinants of [Arg2]PTH-(1-34) binding and signaling in the transmembrane region of the parathyroid hormone receptor.
AUTHOR: Gardella T J; Juppner H; Wilson A K; Keutmann H T; Abou-Samra A B; Segre G V; Bringhurst F R; Potts J T Jr; Nussbaum S R; Kronenberg H M
CORPORATE SOURCE: Endocrine Unit, Massachusetts General Hospital, Boston.
SOURCE: Endocrinology, **(1994 Sep)** 135 (3) 1186-94.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19941006
Last Updated on STN: 19970203
Entered Medline: 19940926

AB Previously, we reported that [Arg2]PTH-(1-34) bound to the rat osteosarcoma cell line, ROS 17/2.8, with 2-fold higher apparent affinity than it did to the opossum kidney cell line, OK, yet the analog was only a weak partial agonist for cAMP stimulation with ROS 17/2.8 cells, whereas it was a full cAMP agonist with OK cells. These results suggested that the rat and opossum PTH receptors differ in a region recognized by the hormone's amino-terminus. In this report we show that the cloned PTH receptors derived from ROS 17/2.8 and OK cells, expressed in COS-7 cells, also displayed altered responses to [Arg2]PTH-(1-34). Thus, [Arg2]PTH-(1-34) bound to the cloned rat **PTH receptor** with 7-fold higher affinity than it did to the cloned opossum **PTH receptor**, and in cAMP stimulation **assays**, it was a much weaker **agonist** with the rat receptor than it was with the

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890606

AB A canine adenocarcinoma model (CAC-8) of humoral hypercalcemia of malignancy was evaluated for transforming growth factors (TGF)-alpha and -beta, PTH-like activity [adenylate cyclase-stimulating activity (ACSA)], and in vitro bone-resorbing activity. Biological activities present in CAC-8 were separated by reverse phase or cation exchange HPLC. TGF alpha in tumor extract was separated from TGF beta and ACSA by reverse phase HPLC. TGF alpha eluted between 26-30% acetonitrile and was identified by RIA. After the initial reverse phase separation, TGF beta and ACSA in tumor extract coeluted between 36-38% acetonitrile. Sequential cation exchange followed by reverse phase HPLC separated TGF beta from ACSA. Evaluation of fractions containing ACSA using an in vitro bone-resorbing **assay** demonstrated copurification of ACSA and bone-resorbing activity. The **PTH receptor antagonist** [Nle8,18,Tyr34]bovine PTH-(3-34)-amide, but not [Nle8,18,Tyr34]bovine PTH-(7-34)-amide, completely inhibited ACSA in column eluates. Conditioned cell culture medium from CAC-8 primary cultures contained predominantly latent TGF beta that could be activated by acidification. These findings indicate that the CAC-8 model of cancer-associated hypercalcemia produces a PTH-like factor, TGF alpha, and TGF beta that were separable by reverse phase or cation exchange HPLC. This feature should be useful to investigate the role of TGFs and PTH-like proteins in the pathogenesis of humoral hypercalcemia of malignancy.

L5 ANSWER 5 OF 53 MEDLINE on STN
ACCESSION NUMBER: 87296318 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3039857
TITLE: Evaluation of a parathyroid hormone antagonist in an in vivo multiparameter bioassay.
AUTHOR: Horiuchi N; Rosenblatt M
SOURCE: American journal of physiology, **(1987 Aug)** 253 (2 Pt 1) E187-92.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198709
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19870922

AB The antagonist properties of a bovine parathyroid hormone analogue ([Tyr34]bPTH-(7-34) amide were quantitatively assessed in vivo in a multiparameter **assay** to estimate the potency of the antagonist against the major actions of PTH. The analogue inhibited PTH-stimulated urinary excretion of phosphate and adenosine 3',5'-cyclic monophosphate in vitamin D-deficient thyroparathyroidectomized rats in a dose-dependent manner. At a molar dose ratio as low as 5:1 of antagonist to PTH, partial inhibition occurred. PTH stimulates the activity of 25-hydroxyvitamin D3-1 alpha-hydroxylase in renal proximal tubules. When coinfused with PTH, this analogue completely inhibited PTH-stimulated 1 alpha-hydroxylase activity at a molar dose ratio of 25:1 of antagonist to PTH and partially inhibited the activity at a molar dose ratio of 10:1. The analogue revealed no PTH-like agonist activity for stimulation of the 1

Vol. 11, Supp. 1, pp. M503.
ISSN: 0884-0431.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L5 ANSWER 18 OF 53 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:619708 SCISEARCH
THE GENUINE ARTICLE: GN790
TITLE: SOLID-PHASE SYNTHESIS AND BIOLOGIC ACTIVITY OF HUMAN PARATHYROID HORMONE(1-84)
AUTHOR: GOUD N A; MCKEE R L; SARDANA M K; DEHAVEN P A; HUELAR E; SYED M M; GOUD R A; GIBBONS S W; FISHER J E; LEVY J J; RODKEY J A; BENNETT C; RAMJIT H G; CAPORALE L H; CAULFIELD M P; ROSENBLATT M (Reprint)
CORPORATE SOURCE: MERCK SHARP & DOHME LTD, W POINT, PA, 19486; BACHEM INC, TORRANCE, CA, 00000
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (**1991**) Vol. 6, No. 8, pp. 781-789.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have chemically synthesized the full-length, 84 amino acid, human parathyroid hormone (hPTH) on a > 100 mg scale by the Merrifield solid-phase technique of stepwise peptide synthesis using a benzhydrylamine support. The peptide was purified by high-performance liquid chromatography and found to be > 96% pure. The authenticity of the sequence of the synthetic peptide was confirmed by repetitive Edman degradation. Furthermore, tryptic digestion of hPTH generated the predicted fragments. The synthetic full-length hormone was evaluated for biologic activity in **assays** of **PTH receptor** binding and stimulation of adenylate cyclase activity (using bovine renal cortical membranes and rat and human bone cells). Synthetic hPTH(1-84) was found to be highly potent in binding to **PTH receptors** (K(b) = 1-25 nM) and stimulating adenylate cyclase (K(m) = 1-14 nM). The availability of significant quantities of synthetic full-length hPTH and future analogs will permit widespread use in multiple in vitro and in vivo **assays** to delineate their spectrum of biologic properties. Available supplies of the synthetic hormone will also enable evaluation of the effectiveness of PTH **antagonists** at inhibiting the action of native sequence hormone at its receptors.

L5 ANSWER 19 OF 53 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:409633 SCISEARCH
THE GENUINE ARTICLE: FX132
TITLE: MUTATIONAL ANALYSIS OF THE RECEPTOR-ACTIVATING REGION OF HUMAN PARATHYROID-HORMONE
AUTHOR: GARDELLA T J (Reprint); AXELROD D; RUBIN D; KEUTMANN H T; POTTS J T; KRONENBERG H M; NUSSBAUM S R
CORPORATE SOURCE: MASSACHUSETTS GEN HOSP, ENDOCRINE UNIT, BOSTON, MA, 02114 (Reprint); HARVARD UNIV, SCH MED, BOSTON, MA, 02114
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (**1991**) Vol. 266, No. 20, pp. 13141-13146.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH

REFERENCE COUNT: 30
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The first 4 residues of parathyroid hormone (PTH) are highly conserved in evolution and are important for biological activity. We randomly mutated codons 1-4 of human PTH (hPTH) with degenerate oligonucleotides and, after expression in COS cells, **screened** the mutants for receptor binding and cAMP-stimulating activity using ROS 17/2.8 cells. This survey identified Glu4 and Val2 as important determinants of receptor binding and activation, respectively. Positions 1 and 3 were more tolerant of substitutions indicating that these sites are less vital to hormone function. Activities of synthetic hPTH(1-34) analogs further demonstrated the importance of positions 2 and 4. The binding affinity of [Ala4, Tyr34] hPTH(1-34)NH2 was 100-fold reduced relative to [Tyr34]hPTH(1-34)NH2 (K(d) values = 653 +/- 270 and 4 +/- 1 nM, respectively), and [Arg2, Tyr34]hPTH(1-34)NH2 was a weak partial **agonist** which bound well to the ROS cell receptor (K(d) = 31 +/- 10 nm). The Arg2 analog was nearly as potent as PTH(3-34) as an in vitro PTH **antagonist** in osteoblast derived cells. However, unlike PTH(3-34), [Arg2]PTH was a full **agonist** in opossum kidney (OK) cells. These observations suggest that the activation domains of the OK and ROS cell **PTH receptors** are different. Thus, amino-terminal PTH analogs may be useful as probes for distinguishing properties of **PTH receptors.**

L5 ANSWER 20 OF 53 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:342742 SCISEARCH
THE GENUINE ARTICLE: FR446
TITLE: CYCLIC PARATHYROID-HORMONE RELATED PROTEIN ANTAGONISTS - LYSINE-13 TO ASPARTIC-ACID 17 [I TO (I (4)] SIDE-CHAIN TO SIDE-CHAIN LACTAMIZATION)
AUTHOR: CHOREV M (Reprint); ROUBINI E; MCKEE R L; GIBBONS S W; GOLDMAN M E; CAULFIELD M P; ROSENBLATT M
CORPORATE SOURCE: MERCK SHARP & DOHME LTD, W POINT, PA, 19486 (Reprint); HEBREW UNIV JERUSALEM, IL-91120 JERUSALEM, ISRAEL
COUNTRY OF AUTHOR: USA; ISRAEL
SOURCE: BIOCHEMISTRY, (**1991**) Vol. 30, No. 24, pp. 5968-5974.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 52
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cyclization of parathyroid hormone related protein (7-34)amide [PTHrP(7-34)NH2] via covalent bond formation between the epsilon-amino of Lys13 and the beta-carboxyl of Asp17 yielded a 20-membered ring lactam. This analogue, [Lys13,Asp17]PTHrP(7-34)NH2, was 5-10-fold more potent than the linear parent peptide (K(b) = 15 and 18 nM in **PTH receptor** binding **assays**, and K(i) = 130 and 17 nM in PTH-stimulated adenylate cyclase **assays** in bovine renal cortical membrane and in human bone derived BIO cells, respectively). In contrast, a linear analogue in which charges in positions 13 and 17 were eliminated and other stereoisomers of the above-mentioned lactam in which either Lys13 and/or Asp17 were replaced by the corresponding D-amino acids were much less potent with regard to **antagonist** bioactivity than the parent peptide. The rationale for the design of the lactam as well as the conformational implications for the PTHrP sequence in light of reported models suggested for the 1-34 peptide are described. The potential use of conformationally constrained analogues for elucidating the "bioactive conformation" of **antagonists** and for the design of substantially simplified molecular structures for **antagonists** is discussed.

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     FILE 'MEDLINE, CAPLUS, SCISEARCH, BIOSIS, USPATFULL, PCTFULL' ENTERED AT
     17:21:59 ON 11 MAY 2004
L1          3491 S (PARATHYROID(W)HORMONE(W)RECEPTOR?) OR (PTH(W)RECEPTOR?)
L2           375 S L1(S)(AGONIST? OR ANTAGONIST?)
L3           122 S L2(P)(METHOD OR ASSAY? OR SCREEN?)
L4           102 DUP REM L3 (20 DUPLICATES REMOVED)
L5            53 S L4 AND PY<=2000

=>

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